

This Week's Citation Classic

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Krnjević K & Schwartz S. The action of γ -aminobutyric acid on cortical neurones. *Exp. Brain Res.* 3:320-36, 1967. [Wellcome Dept. Res. Anaesthesia, McGill Univ., Montreal, Canada]

When γ -aminobutyric acid is applied to single cortical neurones, it causes changes in membrane potential and conductance that are similar to the effects of synaptic inhibition. It is therefore concluded that this normal constituent of the brain could be the physiological transmitter at inhibitory synapses in the cerebral cortex. [The SC[®] indicates that this paper has been cited over 240 times since 1967.]

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"For the last 25 years, there has been almost unanimous agreement among neurophysiologists that at points of junction ('synapses') nerve cells communicate with each other mainly by releasing specific excitatory or inhibitory substances. Until the 1960s little was known about the identity of the postulated central transmitters. In 1963, John Phillis and myself had reported that, in the cerebral cortex, L-glutamate and γ -aminobutyric acid (GABA) have very powerful and rapid excitatory and inhibitory actions respectively; since both agents are normally present in the cortex in large amounts, we suggested that they may well be physiological transmitters.¹ Without stronger evidence that these effects are similar to the natural synaptic actions, this suggestion was not taken very seriously, especially since there was a wide consensus that these agents could not be neurotransmitters.

"More critical tests required recording from *inside* a cortical neurone while

applying the postulated transmitter just *outside*. In previous attempts, co-axial microelectrodes had not been very satisfactory, because huge 'coupling' artifacts largely obscured any significant effects. A much better possible solution was suggested to me by Robert Werman during my visit to his laboratory in Indianapolis (in 1964): this was to fix microelectrodes side-by-side, thus greatly reducing electrical coupling. He was moreover kind enough to give me two of his Narishige micromanipulators for this purpose.

"Shortly afterwards, I was joined in Montreal by Susan Schwartz (who was then a recent graduate of the Albert Einstein School of Medicine) and we started using these to prepare double micropipettes. There were many technical difficulties, compounded by the scarcity of equipment. I had only just moved into the new, but empty, anaesthesia research laboratories situated in the newly-opened McIntyre Medical Building. The frequency of useful intracellular penetrations was much reduced by the presence of the second external pipette; so it was doubly frustrating when cells were successfully impaled but GABA could not be released in sufficient quantity. On the other hand, GABA's action proved to be exceptionally favourable, since its hyperpolarizing effect became even more evident as cellular potentials deteriorated, while its rapid time course ensured that even during brief intracellular recording there was some chance of making significant observations. Moreover, the large increases in membrane conductance evoked by GABA could be detected even under unpromising recording conditions.

"So we were very fortunate in being able to show that GABA consistently imitates the synaptic inhibitory action and therefore fulfills what is generally accepted as one of the most important criteria by which one identifies a transmitter."

1. Krnjević K & Phillis J W. Iontophoretic studies of neurones in the mammalian cerebral cortex. *J. Physiology* (London) 165:274-304, 1963.